REMARKS

Claims 1, 9-10 and 12 have been amended. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Rejection under 35 U.S.C. § 102(b) Dalemans

Claims 1-6 and 8-12 are rejected under 35 U.S.C. § 102 (b) as anticipated by Dalemans, et al. (WO 99/30733).

The present invention is directed to an immunological composition comprising a protein vaccine component and a negatively charged mineral-based adjuvant which are pre-mixed in combination with a DNA vaccine component which elicits a differentiated immunological response which is a Th1 response against the DNA vaccine component and a Th2 response against the protein component. The two vaccine components are combined for simultaneous administration, without additional adjuvants.

On the other hand, while Dalemans teaches a DNA vaccine component, a protein vaccine component and an mineral-based adjuvant, the mineral-based adjuvant may be positive or negative in charge and is formulated as a ***liposome or with monophosphoryl lipid A*** (Dalemans, page 9, last 2 paragraphs). Furthermore, to the extent that Dalemans teach preincubation of the protein component and the mineral-based adjuvant, Dalemans teach the protein antigen component formulated as a ***slow release*** component and incubated with a ***positively charged*** mineral-based adjuvant (Examples 8 and 9). Furthermore, polycaprolactone is added as an additional adjuvant. Accordingly, Dalemans do not teach adding a ***single adjuvant*** which is a mineral-based and ***negatively charged***.

To clearly distinguish the presently claimed invention from Dalemans, claims 1 and 10 have been amended to closed language "consisting of" in steps (a) and (b). Step (c) clearly recites that a single negatively-charged mineral-based adjuvant is used. Basis for the amendment is found in the Examples. In particular, this amendment is responsive to the Examiner's comments on page 4, paragraph 4 to page 5, paragraph 1 of the Final Office Action. Accordingly,

the present claims cannot be anticipated by Dalemans which teaches additional components, which are excluded from the claims as amended.

Furthermore, Dalemans teach a coating such as poly-caprolactone or poly-lactide-co-glycolide to coat already adsorbed complexes of protein and "alum" to provide a layer that delays release of adsorbed protein after exposure to interstitial fluid after injection which is not part of Applicants' invention and is excluded by the closed language of claims 1 and 10 as amended.

In contrast to the claimed invention, by following the teaching of Dalemans, one of ordinary skill in the art would arrive at either :

(a) a vaccine composition with premixed protein and adjuvant, but as a slow release formulation. In particular, an immunological composition that comprises a DNA and a protein vaccine component, the latter of which is pre-mixed with a ***positively charged*** mineral-based adjuvant and which is formulated as a ***slow release*** component.

(b) a vaccine composition which is not a slow release formulation, but without premixing protein and adjuvant. In particular a combination of any kind of mineral-based adjuvant (indiscriminatorily positively charged or negatively charged) with a DNA and protein vaccine component where adjuvant and protein are not premixed.

Neither of the above options results in the presently claimed invention.

The Examiner asserts that addition of lipid polymers does not serve to enhance the immunological activity of the vaccine, and therefore such components cannot be regarded as adjuvants. However, on page 5, lines 9-11 of Dalemans, it is clearly stated that slow release protein vaccine components (i.e. comprising lipid polymers) enhance the magnitude of the induced immune response. Indeed the exact purpose for administering a slow release protein component is to create a time lag between protein presentation and DNA administration (to allow for the DNA to be expressed, transcribed and translated in order to present the DNA-encoded protein to the immune system at about the same time as the protein vaccine component).

The Examiner remarks that arguments directed to the Th1 and Th2 responses are not persuasive as such features are not recited in the claims (Final Office Action, page 7, last paragraph). Accordingly, claim 1 is amended to recite that "...a polynucleotide immunogenic component ...results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic Th1 immune response: and "a protein antigen immunogenic component ... [induces] a prophylactic or therapeutic Th2 immune response". Claims 9, 10, and 12 have been similarly amended.

In this regard, as previously argued, mineral-adsorbed adjuvated protein vaccinations lead to a Th2 immunological response, characterized by a strong predominance of subtype IgG1 antibodies (see paragraph 0039 of published U.S. application corresponding to pages 7-8, bridging paragraph of the present specification). The immunogenic compositions of the claimed invention provide a sufficient Th1 and a sufficient Th2 response ***within the same vaccine preparation*** which was unexpected in view of the art including Dalemans. By pre-incubating the negatively charged, mineral-based adjuvant with the protein antigen vaccine component prior to formulating with the polynucleotide vaccine component, both a Th1 and a Th2 response is obtained after administration of the vaccine. Furthermore, the antigen for which a Th2 response is desired can be predetermined by using that antigen as the protein antigen adsorbed onto the negatively charged mineral adjuvant, and, in the same vaccine preparation, the antigen for which a Th1 response is predetermined by providing that antigen as the DNA polynucleotide component.

This result is achieved by pre-incubation of a protein antigen with a negatively charged, mineral-based adjuvant. While Dalemans provides a listing of adjuvants on page 9, there is no teaching to direct one of ordinary skill in the art to select a negatively charged mineral-based adjuvant for preincubation with the protein component of the immunogenic composition.

While Dalemans teach both negative and positively charged mineral-based adjuvants, Dalemans does not distinguish between them. The recognition of the different effect obtained by use of a negatively charged mineral-based adjuvant is an important aspect of the invention.

There is an essential difference between the effects brought about by a positively charged adjuvant and a negatively charged adjuvant, not only regarding the interaction with DNA, but also with protein. See the graph on page 6 of the Applicants' application as published (U.S. Publ

no. 2005/0129712) which shows a dramatic difference between the negatively charged mineral-based adjuvant (Aluminum phosphate) and a positively charged mineral-based adjuvant (Aluminum hydroxide). Applicants stress this difference and point out that the Office Action incorrectly refers to aluminum hydroxide as a negatively charged adjuvant whereas aluminum hydroxide is positively charged (see Office Action, pages 3-4, bridging paragraph, referring to Example 9 of Dalemans). The Examiner also states that aluminum phosphate and aluminum hydroxide are equivalent negatively charged mineral-based adjuvants (see Office Action, page 8, last paragraph) which is clearly not the case as aluminum hydroxide is positively charged and has a different effect as shown by the graph on page 6 of the published application of Applicants (U.S. Publ no. 2005/0129712) mentioned above. While one of ordinary skill in the art could distinguish between a positively and negatively charged mineral-based adjuvant, such knowledge would not lead one of ordinary skill in the art to the present invention which requires the selective use of a negatively-charged mineral-based adjuvant in order to obtain the Th1 and Th2 response in the same vaccine which is one of the important features of Applicants' invention.

In order to further support the highlighted differences between positively charged mineral-based adjuvants (such as aluminum hydroxide) and negatively charged mineral-based adjuvants (that is, aluminum phosphate), reference is made to a publication which is co-authored by the inventors of the present application (Kwissa, Lindblad, Schirmbeck & Reimann (2003) "Codelivery of DNA vaccine and a protein vaccine with aluminum phosphate stimulates a potent and multivalent immune response", Journal of Molecular Medicine, vol. 88(8): 502-510; Attachment). Figure 2 of the paper (reproduced below) clearly shows that even if aluminum hydroxide is pre-incubated with protein, which adsorbs readily onto the aluminum hydroxide, it completely suppresses a response to the DNA oligonucleotide, leaving it non-functional in respect of immunogenicity (see groups 2-4 and 10-12 of Figure 2). Accordingly, by following the teaching of Dalemans with respect to a positively charged mineral-based adjuvant indiscriminately, one of ordinary skill in the art would basically disable the DNA component of the vaccine.

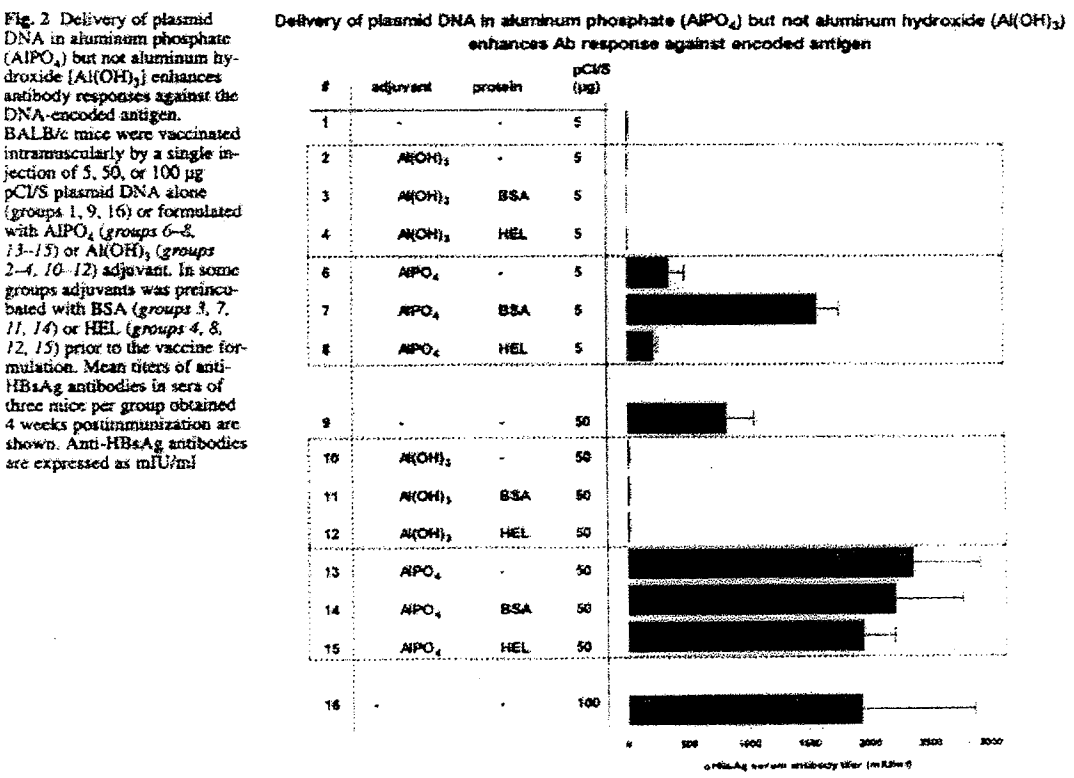

Fig. 2 Delivery of plasmid DNA in aluminum phosphate ($AlPO_4$) but not aluminum hydroxide [$Al(OH)_3$] enhances antibody responses against the DNA-encoded antigen. BALB/c mice were vaccinated intramuscularly by a single injection of 5, 50, or 100 μg pCI/S plasmid DNA alone (groups 1, 9, 16) or formulated with $AlPO_4$ (*groups 6–8, 13–15*) or $Al(OH)_3$ (*groups 2–4, 10–12*) adjuvant. In some groups adjuvants was preincubated with BSA (*groups 3, 7, 11, 14*) or HEL (*groups 4, 8, 12, 15*) prior to the vaccine formulation. Mean titers of anti-HBsAg antibodies in sera of three mice per group obtained 4 weeks postimmunization are shown. Anti-HBsAg antibodies are expressed as mIU/ml

As set forth in M.P.E.P. 2121.01:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ." *In re Hoeksema,* 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v.* **>*Mayo Found. For Med. Educ. & Research*<, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) ...

The teaching of Dalemans is non-enabling with respect to the claimed invention which is the use of mineral adjuvants in combination with a single formulation comprising a DNA vaccine component and a protein vaccine component. Dalemans, in essence, teaches only the use of a positively-charged mineral adjuvant in combination with a protein vaccine in the context of a slow release formulation.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

All amendments are made without prejudice to the possibility of future reinstatement of any excluded matter and/or subsequent filing of divisional applications based on any matter contained in the application as field. Any amendments made by way of the present response, and the observations contained herein, are made solely for the purposes of the prosecution of the US patent application and without prejudice to the applicant to other jurisdictions and/or other patent applications.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Jan. 21, 2010

By: Che Chereskin

Che Swyden Chereskin, Ph.D.
Registration No. 41,466
Agent of Record
Customer No. 20,995
(949) 721-6385

8405839_2
012110